# Progressive familial intrahepatic cholestasis with normal GGT level appearing with lichenification and enlargement of hands and feet

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**Progressive familial intrahepatic cholestasis is a serious disease of the liver, known as Byler disease, characterized by hepatocellular cholestasis. Severe pruritus and high serum bile acid concentrations are the most important diagnostic criteria of this autosomal recessive inherited disease. Here, we present a five-year-old boy with lichenification and enlargement of hands and feet as a sign of progressive familial intrahepatic cholestasis due to severe pruritus.**

***Key words: progressive familial intrahepatic cholestasis, GGT, enlargement of extremities.***

Progressive familial intrahepatic cholestasis (PFIC), formely known as Byler disease, is characterized by progressive hepatocellular cholestasis with autosomal recessive inheritance. Cholestasis typically begins in infancy and the patients progress to cirrhosis by the second decade of life. Severe pruritus and high serum bile acid concentrations are the clinical diagnostic criteria of the disease[1].

Progressive familial intrahepatic cholestasis is differentiated into three separate syndromes in accordance with recent molecular and genetic studies. PFIC type I and type II are characterized by low or normal gamma-glutamyl transpeptidase (GGT) levels, while high GGT levels are descriptive for PFIC type III[2-4].

In cases with PFIC, cutaneous mutilation, excoriations and lichenification of the skin have been reported due to severe pruritus. Recently, lichenification and enlargement of hands and feet have been described in three patients as a sign of PFIC with normal GGT levels[5].

We present here another case with lichenification and enlargement of hands and feet as a sign of PFIC, who also had normal GGT levels.

### *Case Report*

A 4.5-year-old boy was brought to our hospital with a history of jaundice and severe pruritus. He was a full term neonate with a birth weight of more than 2.5 kg. He was noticed to be jaundiced at 2.5 months of age with dark urine and pale stool. He was hospitalized several times because of relapsing course of icterus, sometimes associated with diarrhea. The pruritus became progressively worse in the last six months, with the child excessively scratching and scraping his hands and feet throughout the day and especially at night.

Family history revealed that the parents were first cousins and that he had two healthy older brothers. It was also noted that his eldest brother had died at two months of age with jaundice, nine years previously.

Clinical examination revealed his height as 90 cm (H SDS: -3.15) and weight 14 kg (W SDS: -1.07). He was icteric and itchy with bloody excoriations noted on the body. The skin on both hands and feet was thickened, lichenified and rough, and the fingers and toes were enlarged, stubby and broad (Fig. 1). His abdomen was soft and distended, with a firm liver palpable 6 cm and a spleen 2 cm below the costal margin.

Laboratory evaluation showed the following values: hemoglobin 13 g/dl; leukocyte count 17,800/mm$^3$; platelet count 450,000/mm$^3$; alanine aminotransferase (ALT) 134 U/L (0-41); aspartate aminotransferase (AST) 177 U/L (0-37); GGT 21 U/L (21-55); alkaline

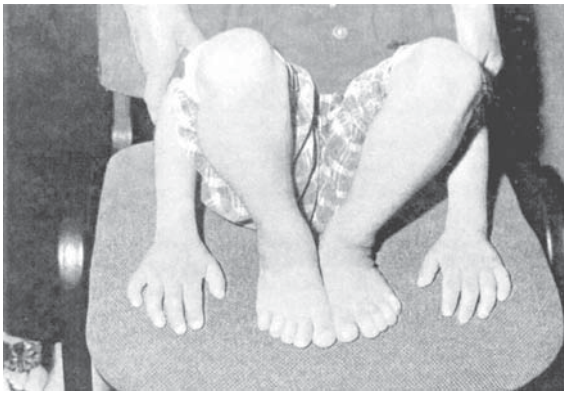

**Fig. 1.** Lichenification and enlargement of hands and feet.

phosphatase (ALP) 352 U/L (80-640); total bilirubin 7.4 mg/dl; conjugated bilirubin 4.5 g/dl; cholesterol 200 mg/dl (60-200); triglyceride 284 mg/dl (40-180); total protein 7.8 g/dl; albumin 3.4 g/dl; calcium 9.6 mg/dl; glucose 106 mg/dl; prothrombin time 17 seconds (12-14); and partial prothromboplastin time 46 seconds (25-38). A repeat coagulation profile was in normal limits after intramuscular 3 mg vitamin K administration. Alpha-1-antitrypsin level, blood amino acid analyses and viral markers of some hepatotrophic agents (Toxoplasma gondii, rubella virus, cytomegalovirus, herpes virus, Epstein-Barr virus, hepatitis B virus and hepatitis C virus) did not reveal any abnormalities. Thoracal and vertebral X-rays were also normal. Serum bile acid concentration was markedly increased: 190 $\mu$mol/L (0-10). Abdominal ultrasonography showed mild hepatosplenomegaly.

Liver histology on light microscopy showed partial obliteration of normal architecture. Widening of portal tracts having mixed inflammation, with porto-portal septae in some areas, and early, incomplete nodule formations were noted. Hepatocytes were hydropic with coarse bile stasis. Rare giant cells, rosette formations and canalicular dilatations were seen. There was mild peripheral cholangiolar proliferation without bilirubinostasis in portal areas and septae (Figs. 2, 3a, 3b, 4).

On ultrastructural examination, coarse granular Byler type bile was detected (Fig. 4). Although the light microscopic histology of cirrhotic progression was suggestive of PFIC type I or II, electron microscopy revealed the presence of type I (Byler type) bile, and the case was diagnosed as an unusual variant of PFIC type I (Fig. 5).

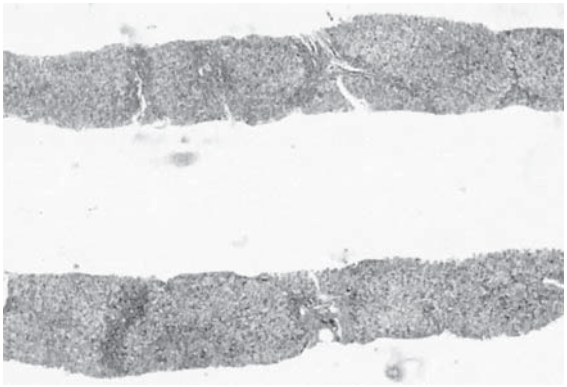

**Fig. 2.** Liver architecture was partially distorted (H&E x 12.5).

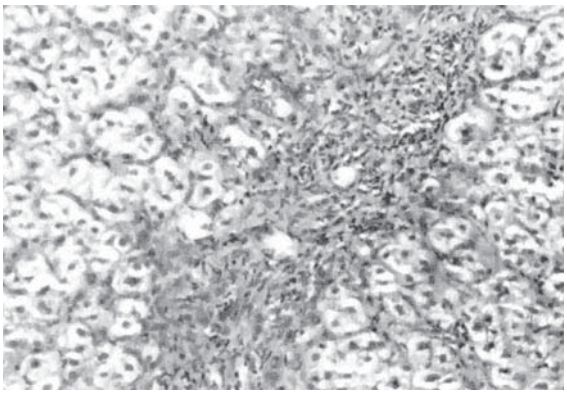

**Fig. 3a.** Portal mixed inflammation and cholangiolar proliferation (H&E x 100).

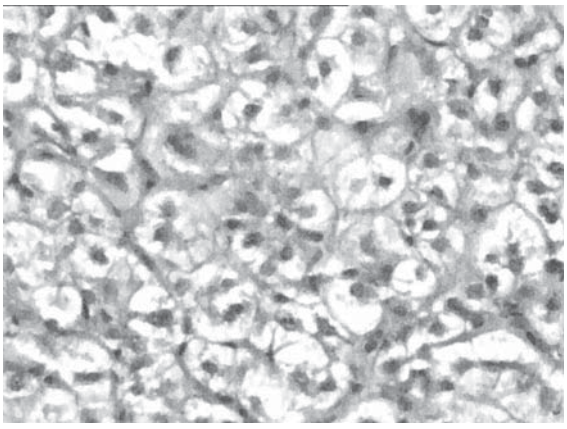

**Fig. 3b.** Hepatocellular and canalicular bile stasis (H&E x 200).

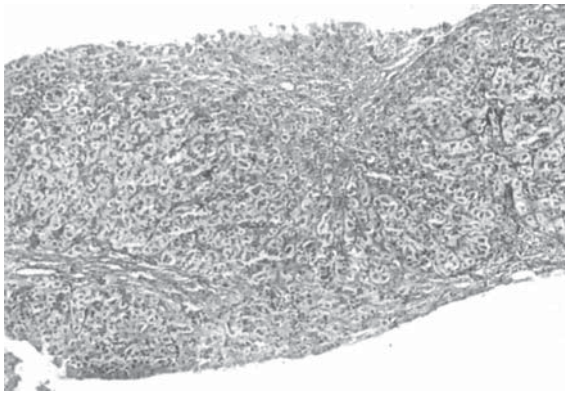

**Fig. 4.** Collagenized fibrous tissue in portal-periportal septae (trichrome stain x 40).

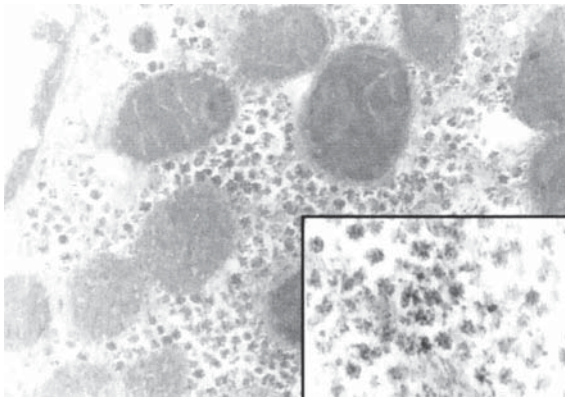

**Fig. 5.** Coarse granular bile [electron microscopy (EM) x 20000 (inset 85000)].

Ursodeoxycholic acid (20 mg/kg daily), vitamins A, D, E, K, and skin moisturing lotions were started. After three months, skin changes and pruritus had subsided. Hepatosplenomegaly diminished after 12 months and there were significant decreases in mean serum levels of ALT (38 U/L), AST (53 U/L), total bilirubin (0.5 mg/dl) and conjugated bilirubin (0.3 mg/dl). No adverse effect of ursodeoxycholic acid treatment was found.

## Discussion

In the patient reported here, severe pruritus and jaundice were the characteristics of cholestasis. Intrahepatic cholestasis is more frequent than extrahepatic cholestasis in childhood. In fact, ultrasonography and liver biopsy excluded extrahepatic cholestasis in this patient. In intrahepatic cholestasis with morphologic changes of intrahepatic bile ducts, such as paucity of interlobular bile ducts and sclerosing cholangitis, severe hypercholesterolemia, and high levels of ALP and GGT are expected. In addition, there are many causes of intrahepatic cholestasis without morphologic changes of intrahepatic bile ducts: chromosomal disorders, Aagenaes syndrome (hereditary lymphedema with recurrent cholestasis), hypothyroidism, peroxisomal disorders, Niemann-Pick disease, alpha-1-antitrypsin deficiency, cystic fibrosis, galactosemia, fructose intolerance and tyrosinemia[1]. Clinical and laboratory findings of this case including liver biopsy were not consistent with these disorders.

Inborn errors of bile acid biosynthesis are another group of metabolic causes of intrahepatic cholestatis. Normal serum bile acid levels in spite of apparent cholestasis is the striking evidence for these disorders[1]. Cholesterol and GGT levels are normal, suggesting Byler disease in isomerase deficiency, one of the bile acid biosynthesis defects, but pruritus is not expected. Another, 5-beta reductase deficiency, presents with high GGT levels.

In the case described here, parental consanguinity and history of jaundice in the eldest sibling who died at the age of two months were suggestive of an autosomal recessive condition. In addition, high levels of serum bile acid, normal levels of GGT and cholesterol, severe pruritus and jaundice indicated PFIC type I or type II.

The term PFIC has been used for patients with the following criteria: chronic unremitting hepatocellular cholestasis, exclusion of identifiable metabolic or anatomic disorders, an occurrence pattern consistent with autosomal recessive inheritance, and a characteristic combination of clinical, biochemical and histologic features. PFIC typically presents in the first six months of life with cholestasis, hepatomegaly, severe pruritus, growth failure and fat soluble vitamin deficiency[1,6].

Progressive familial intrahepatic cholestasis type I and type II have similar clinical presentations although persistent cholestasis, secretory diarrhea and bouts of pancreatitis are suggestive for type I. There are mutations on chromosome 18q 21-22 in the FIC-I gene in type I that result in defective transport of aminophospholipid. PFIC type II has mutations in the gene found on chromosome 2q 24 which encodes bile salt export pump (BSEP)[7,8]. On the other hand, PFIC type III cases have

high levels of GGT and mutations in the p-glycoprotein multi-drug resistance 3 (MDR-3) gene[2]. In other words, specific defects in the FIC-1, BSEP and MDR-3 gene are responsible for distinct PFIC phenotypes.

In patients with different types of PFIC, histology of liver tissue reveals hepatocanalicular cholestasis, fibrosis, bile duct injury, loss of paucity of interlobular bile ducts and portal inflammation[9]. Electron microscopy reveals the coarsely granular bile found in dilated canaliculi that lack villi in PFIC type I and amorphous or finely filamentous bile in PFIC type II[1,5,10,11].

In this patient, history of diarrhea and electron microscopic findings were suggestive of PFIC type I, although genetic analysis could not be performed. In differential diagnosis, alpha-1-antitrypsin deficiency was excluded immunocytochemically and by periodic acid-Schiff (PAS) stain with/without diastase. Viral infections were not considered since portal inflammation was dominant and giant cells were scarce. In addition, there were no cytoplasmic or nuclear inclusions. Benign recurrent intrahepatic cholestasis was not considered because of both clinical and histopathological features.

The first report of intrahepatic cholestasis in childhood in our country was about two fatal cases, published in 1976[12]. There was also a report regarding 24 Turkish children with intrahepatic cholestasis including Byler disease treated with ursodeoxycholic acid, 15-20 mg/kg daily for 12 months. It was concluded that ursodeoxycholic acid was a safe and effective treatment with significant improvement in children with intrahepatic cholestasis[13]. Similar outcomes were reported by Jacquemin et al.[13] with ursodeoxycholic acid 20-30 mg/kg peroral for a period of 2-4 years in 39 children with PFIC. As it was found effective and well tolerated in resolving or improving the liver function and clinical status of most cases, ursodeoxycholic acid was recommended in the initial therapeutic management of children with PFIC[14]. The clinical and biochemical improvement of our case seems to be related to ursodeoxycholic acid therapy. Ursodeoxycholic acid, a tertiary bile acid, is also a choleretic agent. It exerts its beneficial effect in liver disease through a diverse, probably complementary array of mechanisms[15]. So far, direct hepatoprotective and immuno- modulating effects may also have an important therapeutic role[13].

The distinctive appearance of the hands and feet of this case is not a common finding of cholestasis in childhood. Lichenification of the hands and feet and enlargement of the fingers and toes were first described by Ooi et al.[5]. We suggest that lichenification of the hands and feet and enlargement of the fingers and toes need to be considered as a striking clinical feature of PFIC with normal GGT.

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